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Function of the HOX-11 Homeobox Proto-oncogene in the Cell Cycle

It is generally believed that the human cancers have resulted from genetic changes in cellular proto-oncogenes that play an important role in cell growth and differentiation. Increasing evidence suggests that non-randomly acquired chromosomal translocations constitute an important mechanism for proto-oncogene deregulation. The best-studied examples are chromosomal translocations involving the *c-myc* gene in Burkitt's lymphomas, the *bcl-2* gene in non-Hodgkin's follicular lymphomas, and the *bcr-abl* fusion in chronic myelogenous leukemias as well as in some acute leukemias. These studies have established an important paradigm whereby cellular genes involved in the control of cell growth and differentiation may be converted to oncogenic forms by chromosomal translocations that alter their structure or expression. The mechanisms through which leukemias and lymphomas are developed upon deregulation or mutation of oncogenic transcription factors are not well understood, nor is the relationship among the transcription factors to each other in oncogenesis. We and others have cloned the HOX-11 proto-oncogene deregulated by the t(10;14) chromosomal translocation recurring in a subtype of T-cell leukemia. In this study we will test the hypothesis that the HOX-11 proto-oncogene plays a role in cell cycle progression. By using molecular biology techniques, we will over- and under-express this unique proto-oncogene in T-cells as well as of other lineages. The effects of over- and under-expression on cell cycle progression will be examined. It is expected that over-expression of this gene will drive resting cells to progress through the cell cycle, while under-expression will block cell cycle progression of dividing cells. This study will most likely provide us with much knowledge about the molecular events leading to leukemia formation.

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The Role of K^+ Channels in T Cell Activation and Lympho Proliferation

Potassium channels are membrane pore structures that are selectively permeable to potassium ions. Several types of potassium channels on excitable cells are also found on cells of the immune system, most notably thymocytes and T lymphocytes. The expression of these channels appears to be regulated during development, differentiation, and activation of T cells by a foreign aggression. Thus, a specific potassium channel repertoire plays a critical role in the development and maintenance of T lymphocyte immunological functions. By means of molecular biology approaches, we have recently succeeded in the isolation and characterization of potassium channel structures in human T lymphocytes. The long term goals of our research are to elucidate the role of these potassium channel isoforms in T cell functions as well as to design alternative therapeutic strategies for immunosuppression and treatment of lymphoproliferative, inflammatory or autoimmune disorders. Using molecular and biophysical tools, we intend in this research project to investigate the role and the relative contribution of the potassium channel subtypes in T cell functions. We plan to examine in depth, how potassium channels affect the T cell calcium signals. We will also evaluate the role of the potassium channel isoforms in T cell proliferation. The expression and the gene organization of the potassium channel subsets will be investigated in T cell samples from patients suffering from lymphoproliferative diseases. This research project is expected to provide better understanding of the T cell functions and of the role of potassium channels in lymphoproliferation. It will also facilitate the identification of selective therapeutic agents that could treat a variety of T cell-mediated disorders such as lymphoproliferative, inflammatory or autoimmune diseases and to prevent graft rejection.